REMARKS

Claims 25, 28, 39, 42-55, and 57-81 are pending. Claims 25, 42-43, and 57 have been amended and support can be found throughout the specification and claims as originally filed, including for example at page 9, lines 18-19 and page 21, lines 13-15.

With respect to all claims, Applicants have not dedicated, disclaimed, or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Double Patenting

The Examiner has provisionally rejected claims 25, 28, 39, 42-55, and 57-81 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 24-28 and 52-100 of copending Application No. 11/533,709. Applicants respectfully request that the Examiner hold this rejection in abeyance until notice of allowable subject matter.

Rejection under 35 U.S.C. §112, first paragraph – Written description

Claims 25, 28, 39, 42-55, and 57-81 have been rejected under 35 U.S.C. §112 as allegedly failing to comply with the written description requirement. The Examiner alleges that both

> the specification (pages 35-36) and the art indicate that in order to produce heteromultimers that meet the limitations of the claims, the three-dimensional structure of the heteromultimer must be known down to the resolution of individual atoms by such techniques as X-ray crystallography, and determining the geometrical fitting of two (or more) polypeptide molecules in a protein-protein interaction is exceedingly complex and requires the knowledge of using pairs of critical points in combination with an adequate description of the respective molecular surfaces of the two polypeptides (Norel *et al.*, page 933; see also Figure 1). [emphasis added] (*Id.* at pages 4-5).

In addition, the Examiner states that

> one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by members of the genus, because the pairing of only 4 specifically numbered amino acid positions in the C_H3 antibody constant domain region is not representative of the claimed genus. (page 5 of the October 2, 2008 Office Action)

Applicants respectfully disagree and submit that when the proper legal standard for the written description requirement is applied, the pending claims are in compliance with the requirement. As such, Applicants respectfully request reconsideration by the Examiner and a withdrawal of the rejection.

A. The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph, is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language" (*In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983; *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. (*See, e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000; *See also* M.P.E.P. §2163 II(A)).

With regard to biomolecules, M.P.E.P. §2163 II A. 3. (a) provides that the U.S. Court of Appeals for the Federal Circuit has explained that

> "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must

contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also *Capon v. Eshhar*, 418 F.3d at 1358, 76 USPQ2d at 1084 (Fed. Cir. 2005).

Furthermore, the Court in *Falkner* acknowledged that the recitation of known sequence information would not serve the purpose of the written description requirement and the "forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification" (*Falkner* 448 F.3d at 1368).

B. Application of the Legal Test for Written Description

As currently amended, claim 25 recite "wherein the first and second polypeptides each comprise an antibody constant domain". Applicants respectfully submit that when the legal standard described above is applied, it must be found that the disclosure of the instant specification reasonably conveys to a person of ordinary skill in the art that the Applicants had possession of the genus of heteromultimers recited by claim 25, as currently amended.

Support for the genus can be found in the instant specification and in the relevant scientific literature concerning three-dimensional nature of antibody constant domains at the time of filing. For example, figure 5 provides the interface residues for various antibody constant domains, including those suitable for manipulation to provide an engineered interface; Figure 6 provides interface residues for various antibody subtypes; and Figure 9 provides a three-dimensional depiction of the protein-protein interaction of a C_H3 dimer based upon the structure of human IgG1 Fc (Deisenhofer, *Biochem.* 20:2361 (1981)). The specification also provides well-known information about the side chain volumes for the amino acid residues in, for example, Table 1 on page 20, and protocols for practicing the present invention (pages 25-56 and the Examples).

Applicants submit that at the time of filing the public domain contained other reports concerning the three-dimensional structure of antibody constant domains. Submitted herewith, for example, are Thies *et al.*, *J Mol Biol.*, 1999 Oct 15;293(1):67-79 which used X-ray crystallography to analyze folding of an Ig C_H3 domain; and Jefferis *et*

al. Immunol Rev., 1998 Jun;163:59-76 that provides a review of the interaction sites in the Fc region of human Ig for effector ligands, including a discussion of the topographical distribution of ten such sites. As stated in *Falkner*, the recitation of such public information in the Applicants' specification would not serve the purpose of the written description requirement.

In addition, the authors of Norel *et al.* (cited by the Examiner) report that a simple and straightforward modification of a well-known matching algorithm using surface complementarity between receptor and ligand protein molecules was successful. (Abstract) For instance, the authors indicate that out of the "16 protein-protein complexes we have tried, 15 were successfully docked" and the "entire molecular surfaces were considered, with absolutely no additional information regarding the binding sites" (Abstract). Therefore, straight-forward and predictable protocols for examining protein-protein three-dimensional protein-protein interactions were likewise available.

Based on the specification and publically available scientific knowledge at the time of filing, a person of ordinary skill in the art could (i) utilize known three-dimensional structural information for antibody constant domains provided by the instant specification and in the public domain, (ii) introduce any necessary site-directed mutations in the amino acid sequence, (iii) express and obtain the antibody constant domains using established cell lines and protocols, in order to form the heteromultimers of the present invention. The three-dimensional structural information for antibody constant domains is well-known to those of ordinary skill in the art, and therefore need not be disclosed for purposes of supporting the genus contemplated by the currently pending claims.

Withdrawal is respectfully requested.

Rejection under 35 U.S.C. §112, second paragraph – Definiteness

The Examiner has rejected claims 25, 28, 39, 42-55, and 57-81 under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention (page 6 of the October 2, 2008 Office Action). The Examiner asserts that the phrase "'greater ratio of heteromultimer: homomultimer forms than for a multimer' is vague and confusing since the terms homomultimer and multimer have no anteceedent basis" (page 6 of the October 2, 2008 Office Aetion). Applicants respectfully disagree and traverse the rejection.

Applicants believe that the terms "a greater ratio of heteromultimer:homomultimer" and "multimer" do not require antecedent basis as each appears for the first time following the article "a". A person of ordinary skill in the art would appreciate that the term "multimer" means the association of two or more polypeptides (either the first or the second polypeptide) and the term "homomultimer" means the association of two or more of the same polypeptide (either the first or the second polypeptide). As such, Applicants submit that claim 25 and all claims depending therefrom are clear and definite. Applicants respectfully request the withdrawal of the rejection.

Rejection under 35 U.S.C. §102

The Examiner has rejected claims 25, 28, 42-43, 45-47, 51, 53-54, 66, and 68 under 35 U.S.C. §102 (a) as allegedly being anticipated by Zhang *et al.* (1994) *Mol. Cell. Biol.*, 14(6):4311-4323 (hereinafter referred to as "Zhang"). The Examiner has rejected claims 25, 28, 39, 42-43, 45-47, 51-55, 66-69, 71-73, 75-78, and 81 under 35 U.S.C. §102 (b) as allegedly being anticipated by Tso *et al.* WO 93/11162 (hereinafter referred to as "Tso") in light of Goodman *et al.* (1991) *Biochemistry*, 30:11615-11620 and Landschulz *et al.* (1988) *Science*, Jun 24, 1988: 240:1759-1764. Applicants respectfully disagree and traverse the rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

As currently amended, claim 25 recites "wherein the first and second polypeptides each comprise an antibody constant domain". With regard to Zhang and Tso, Applicants submit that neither reference teaches or suggests this element. As neither Zhang nor Tso teach or suggest all the claims elements of pending claim 25, neither can anticipate claim 25, or any other claim depending therefrom. Therefore, Applicants respectfully request the withdrawal of the rejection.

CONCLUSION

In light of the above amendments, Applicants believe that this application is now in condition for immediate allowance and respectfully request that the case be passed to issue.

Please charge any fees that might become applicable, including any fees for extension of time, or credit overpayment to Deposit Account No. 50-4634, referencing Attorney's Docket No. GNE-0321C2 (P0927C2) (123851-183886).

Respectfully submitted,
GOODWIN PROCTER LLP

Dated: March 24, 2009 By: J. P. Bernhardt
Jeffery P. Bernhardt
Registration No. 54,997

Address all correspondence to:

GOODWIN PROCTER LLP
135 Commonwealth Drive
Menlo Park, CA 94025s
Tel: (650) 752-3100
Fax: (650) 853-1038

LIBC/3556247.1